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METABOLIC RESPONSES TO SWIMMING EXERCISE IN THE INFECTED RAT.(U)

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Metabolic responses to swimming exercise in the infected rat

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Running Title: METABOLISM DURING EXERCISE AND INFECTION

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council. The facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Bacterial infections cause a reduction in physical performance capacity. Studies were performed to determine if alterations in fuel reserves or energy substrate utilization might explain these decrements in performance. Untrained rats found adaptable to the swim task were divided into sedentary and exercised groups. These groups were subdivided into fed, fasted and fasted-infected rats. Fed rats were used for baseline values. Fasted rats were studied at 24, 48 and 72 h after removal of food and inoculation with heat-killed <u>Streptococcus pneumoniae</u> . Fasted-infected rats were injected with an equal number of viable		

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bacteria and studied at the same time intervals. All exercised groups were studied immediately following a 2-h swim or swim-induced exhaustion. In the absence of infection, fed- and fasted-sedentary and exercise parameters were compatible with previously reported values. Infection caused depletion of glycogen stores, hyperglycemia, hypolipidemia, inhibition of ketone body accumulation and increased circulating plasma insulin and glucagon despite concurrent fasting. Exercise superimposed on infection and associated anorexia amplified these aberrations. Superimposed exercise did not alter the direction of infection-induced changes, but did alter the magnitude of metabolic responses. It was not possible, however, to relate alterations in fuel metabolism directly to reduction in performance.

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Abstract

Bacterial infections cause a reduction in physical performance capacity. Studies were performed to determine if alterations in fuel reserves or energy substrate utilization might explain these decrements in performance. Untrained rats found adaptable to the swim task were divided into sedentary and exercised groups. These groups were subdivided into fed, fasted and fasted-infected rats. Fed rats were used for baseline values. Fasted rats were studied at 24, 48 and 72 h after removal of food and inoculation with heat-killed Streptococcus pneumoniae. Fasted-infected rats were injected with an equal number of viable bacteria and studied at the same time intervals. All exercised groups were studied immediately following a 2-h swim or swim-induced exhaustion. In the absence of infection, fed- and fasted-sedentary and exercise parameters were compatible with previously reported values. Infection caused depletion of glycogen stores, hyperglycemia, hypolipidemia, inhibition of ketone body accumulation and increased circulating plasma insulin and glucagon despite concurrent fasting. Exercise superimposed on infection and associated anorexia amplified these aberrations. Superimposed exercise did not alter the direction of infection-induced changes, but did alter the magnitude of metabolic responses. It was not possible, however, to relate alterations in fuel metabolism directly to reduction in performance.

Key words: Swimming; exercise; bacterial infection; rats; tissue glycogen; oxygen consumption; plasma glucose; free fatty acids; ketone bodies; insulin; glucagon; blood lactate

PREVIOUS STUDIES HAVE DEMONSTRATED that bacterial infections reduce physical work capacity in rats (7, 12), but little is known regarding the impact of exercise on energy substrate stores or their utilization during infection. Studies were performed to clarify the combined effects of swimming exercise and Streptococcus pneumoniae infection on metabolic responses and their relationship to infection-induced performance decrements.

Neufeld and others (23, 31, 33) previously described a pneumococcal sepsis model used in rats. These investigators measured the following metabolic parameters in fed, fasted, and fasted-infected rats: rectal temperatures and plasma concentrations of zinc, ketone bodies (β -hydroxybutyric acid and acetoacetic acid), free fatty acids, insulin and glucagon.

When fasted-noninfected rats were compared to fed-noninfected animals, fasting caused lowering of body temperatures, a slight decrease in plasma zinc and marked increases in ketone bodies and free fatty acids (FFA). Plasma insulin decreased during fasting in noninfected animals, but there was little or no change in plasma glucagon. This resulted in a decrease in the insulin:glucagon molar ratio (23).

Pneumococcal infection in fasted rats caused a reduction in plasma zinc levels, an elevation in rectal temperature, impaired ketonemia, decreased concentrations of plasma FFA and increased plasma insulin and glucagon values, when compared to fasted-noninfected rats (23). Other investigators have reported alteration in glucose metabolism (31), elevated rates of O_2 consumption (32) and aberrations in tissue glycogen stores (8) associated with the catabolic aspects of S. pneumoniae sepsis in rats.

The short-term catabolic aspects of acute swimming exercise have been reviewed by Dawson and Horvath (10). Swimming has been found to increase O_2 consumption (10, 19), deplete tissue glycogen reserves (5, 6, 10, 15) and cause hypoglycemia (6) or hyperglycemia (18), while causing variations in blood lactate values (10), depending on water temperature and duration and intensity of the swim. Several investigators (6, 15, 18) have reported an exercise-induced increase in plasma FFA concentrations; this reached 526 μ Eq/liter for rats forced to swim 2 h (18). Conlee et al. (6) demonstrated a decrease in plasma insulin from 47.3 μ U/ml for fed-sedentary rats to 14.2 μ U/ml following a 2-h swim, while plasma glucagon increased from 53 pg/ml in controls to 117.1 pg/ml in exercised rats.

The present report describes several studies which demonstrate the influence of swimming during a S. pneumoniae infection on O_2 consumption, tissue glycogen content, and plasma glucose, FFA, ketone bodies, insulin and glucagon concentrations.

MATERIALS AND METHODS

Animals. Animals were male, Fisher Dunning rats (F-344, F, MA Bioproducts) weighing 150-200 g. They were maintained on a commercial diet (Wayne-Blox, Allied Mills, Inc.) until the beginning of the experiment and were housed 6 rats per cage in rooms maintained on a 0600-1800 hours light cycle at $23 \pm 1^\circ\text{C}$ with food and water ad libitum. All rats were acclimated for at least 7 days prior to experimentation.

Familiarization. Previous studies by this laboratory (7) indicated that experience with the swimming task was an important factor; 40% of naive Fisher Dunning rats required immediate removal from swim barrels to protect them from sudden death (28). Rats used in these studies

were first screened by a 60-min familiarization swim 7 days prior to experimentation. Rats unable to complete the 60-min swim were not used. This single swim test did not constitute a training-type exercise regimen and therefore data derived beginning one week after this screening test were interpreted as information from untrained rats in response to acute exercise. Following the screening test, adaptable rats were randomly assigned into two major groups: sedentary and exercised. These groups were further subdivided into fed, fasted and fasted-infected subgroups. Fed rats were used for baseline values (0-h time point in the figures).

Infection. Rats were inoculated subcutaneously (sc) in the groin pouch with 2.1×10^2 virulent colony-forming units (CFU) of S. pneumoniae type Ia5 per 100 g body weight. Fasted-noninfected rats received an equal number of heat-killed organisms. All food was removed at the time of inoculation from both fasted-noninfected and -infected groups. The presence of infection was monitored by elevation in body temperature and depression of plasma zinc values.

Swimming. Exercised rats were forced to swim continuously for 2 h in steel barrels filled with tap water maintained at a depth of 55 cm and 33-35°C. Animals swam 5 per barrel to insure vigorous activity. Performance was defined as the time spent swimming in minutes. All swimming was closely monitored by an experienced technician. Exhaustion was arbitrarily taken as 10 sec below the water surface. Ten rats per subgroup were studied at 24, 48 and 72 h postinoculation and immediately after the 2-h swim or at the time of exhaustion in an individual rat. Sedentary subgroups were sacrificed prior to their respective exercised groups.

Blood and tissue sampling. Rats were studied individually; exercised rats were sacrificed within 2 min of completion of the swim. Following anesthesia with halothane, 8 ml of blood were obtained through a thoracotomy by incision of the vena cava using heparinized pipettes. Blood was placed in 15-ml polypropylene tubes; a 500- μ l aliquot was withdrawn and deproteinized separately with 500 μ l of 10% trichloroacetic acid to prevent lactate degradation; a 1-ml aliquot was inactivated separately with 50 μ l aprotinin (Trasylol, FBA Pharmaceuticals, New York, 10,000 kallikrein inactivator units/ml) to prevent proteolysis of glucagon. The remaining heparinized blood was centrifuged and the plasma stored at -20°C until analysis.

Tissue samples (approximately 1 g) of heart, liver and gastrocnemius muscle were quickly excised (within 1 min of anesthesia) and placed in preweighed glass test tubes containing 30% KOH maintained at 90°C. Tubes were heated to 100°C for 2 h to dissolve tissue for glucagon assay. For carcass glycogen measurement, viscera and skin were removed, the carcass weighed, cut into small pieces then ground in a Waring blender containing 30% KOH. The suspension was decanted into glass beakers and placed in 100°C water for 2 h (30). Triplicate 4-ml samples of resultant solution were assayed for glycogen determinations.

Analytical procedures. Oxygen consumption studies were performed as a separate experiment, since rats could not be used immediately following exercise to obtain blood and tissue samples for substrate assays. Mean oxygen uptake was obtained for wet (30-sec immersion), fed, fasted and fasted-infected rats ($n = 4$) prior to a 2-h swim (resting state) and again immediately following a bout of exercise. Each rat acted as its own control. A closed circuit system similar to that described by Moses (21) was utilized in these studies. The

chamber volume (4.7 liters) was small enough to provide quick equilibration and postexercise (for a 15-min period) determination of oxygen consumption using a 1-liter Collins spirometer. Air flow was monitored by a Lab-Crest flow meter at a rate of 4.8 ± 0.3 liters·min⁻¹ (STPD) via a calibrated Collins vacuum motor blower. Calculations were adjusted to take water vapor pressure and body temperature differences of wet rats into consideration (19, 25).

Published procedures were utilized for the determination of tissue glycogen by the hydrolysis method outlined by Good et al. (16), as modified by Sobocinski and Altman (29). Plasma and tissue glucose concentrations were analyzed by the O-toluidine procedure (13). Plasma ketone bodies (20), free fatty acids (9), zinc (26) and insulin and glucagon (24) were assayed as previously described. Insulin:glucagon ratios were calculated as described by Müller et al. (22). Whole blood lactate was assayed by a semi-automatic fluorimetric method (17).

Statistical analysis. Significance of group means was determined by unpaired one-way analysis of variance (ANOVA). A P value of < 0.01 was significant (\ddagger) for fasted-infected versus fasted and (*) for exercised versus sedentary animals. Stressed rats in each study were compared to their appropriate control groups at each selected time interval. Data are presented as the means \pm SE for 10 rats per group.

RESULTS

Body temperature and plasma zinc. Fasting for 24 h (Fig. 1) caused a lowering of body temperature and a slight decrease in plasma zinc values. Progress of the infection was followed by increased rectal temperatures and a further, more marked depression of plasma zinc concentrations. All infected rats were febrile prior to exercise and

other studies. Although temperatures were lower due to water thermal differences following swimming, the rectal temperatures of infected rats were still elevated above fasted values. In both noninfected and infected rats, exercise did not alter plasma zinc concentrations further.

Swimming performance times. Table 1 presents swimming times of infected and noninfected rats at 24, 48 and 72 h postinoculation. The 2-h swim represented about 40% of the rats' maximal capacity (7). Prolonged fasting became slightly detrimental by reducing mean performance duration. There is also an indication of a progressive reduction in swimming times with infection and more than a 61% reduction in performance at 72 h postinoculation by infected rats.

Oxygen consumption. The mean oxygen consumption (Fig. 2) for resting fed rats was $22 \pm 4 \text{ ml/kg} \cdot \text{min}^{-1}$, while for these same rats after the 2-h swim the value was increased to $61 \pm 3 \text{ ml/kg} \cdot \text{min}^{-1}$. Fasting lowered consumption, while infection in the presence of fasting initially increased oxygen uptake, but then decreased it progressively with prolonged sepsis. Results indicate that exercise and infection have a cumulative effect on oxygen utilization.

Blood lactate. Fasting and infection did not alter blood lactate values (Fig. 3) in sedentary rats, while exercise elevated these values in fed, fasted and fasted-infected rats. An overnight fast reduced this increase in both fasted-exercised, noninfected and infected rats. A sharp difference was observed at 48 and 72 h into the fast in noninfected rats (lactate values remained about 12 $\mu\text{mole/ml}$) compared to the infected rats.

Carbohydrate metabolism. Plasma glucose (Fig. 3) concentrations of fed rats were increased about 37% by exercise. Circulating glucose remained relatively constant in both fasted noninfected and infected

sedentary rats. The 2-h swim caused a slight increase in plasma glucose in fasted-exercised noninfected rats and a trend toward increased values in infected rats.

The effects of infection and exercise on tissue glycogen are shown in Table 2. Swimming caused a decrease in heart, liver and muscle glycogen stores in fed-noninfected-exercised rats. Fasting-induced cardiac glycogen accumulation was evident, along with depletion of hepatic and muscle glycogen stores in starved-uninfected sedentary rats. The pneumococcal infection inhibited fasting cardiac glycogen supercompensation, but did not alter loss of liver and skeletal muscle glycogen. Tissue glycogen concentrations were reduced by exercise to the same extent in both fasted-exercised noninfected and infected rats.

Lipid metabolism. Plasma FFA (Fig. 4) increased from 310 μ Eq/liter to 598 μ Eq/liter in response to exercise in fed animals. These data support the work of Askew et al. (1) and others (15, 18, 27). Fasting raised the FFA content, while infection reduced it in sedentary animals. Plasma FFA values were markedly decreased in infected, fasted-exercised rats, but were only slightly diminished in noninfected controls.

Swimming also caused an amplification of fasting ketosis (Fig. 4). During infection, induced ketonemia was diminished in comparison to noninfected controls, but values in fasted-infected-exercised rats were somewhat higher than those of their noninfected counterparts.

Hormone responses. As previously reported (14), exercise decreased plasma insulin and elevated plasma glucagon in fed animals (Fig. 5). Fasting decreased insulin values, but caused little or no change in plasma glucagon. Infection in the fasted rat caused a progressive increase in both insulin and glucagon concentrations. Exercise abated the infection-induced elevation of both.

The insulin:glucagon molar ratios (I/G) are shown in Table 3.

Prolonged fasting reduced these ratios, while the combination of fasting and infection caused a marked depression of fasted values in sedentary rats. Exercise superimposed on fed and fasted noninfected and infected rats resulted in significant reduction below corresponding sedentary I/G ratios.

DISCUSSION

The present studies demonstrate a reduction in physical performance capacity in rats inoculated with S. pneumoniae. Findings are in agreement with previously published data (7, 12) and suggest that alterations in metabolic responses to these stresses may be involved. It should be emphasized that infected rats became progressively less able to exercise for the same length of time as fed and fasted groups. Prolonged fasting reduced swimming times by up to 8%, but could not account for the reduction in performance seen in fasted-infected rats.

Oxygen consumption and blood lactate and tissue glycogen concentrations were used as indices of energy expenditure. In another study (10), the authors indicated that a 2-h swim caused a 3-fold increase in metabolic rate over the basal levels (BMR), with a range in oxygen consumption between 50 and 90 ml/kg·min⁻¹ in exercised rats. It is not entirely clear how the metabolic rate compares to the maximum capabilities of the rat. Data (Fig. 2) for swimming fed rats show a 3-fold increase in oxygen utilization and indicate a submaximal work load (19). One would speculate that both noninfected and infected fasted-exercised rats were exposed to the same submaximal conditions, only the variable time was a factor.

It appears that the added stress of infection resulted in an increased O_2 consumption during the early stages of fever (3). These values decreased with the progressive duration of the infection. This was supported by an inability of the rats to alter early lactic acidosis (Fig. 3) and rising oxygen debt (Fig. 2) brought on by increased anaerobic metabolism during infection and exercise. Alterations in carbohydrate metabolism, although involved, would not seem to explain the decrement in performance, because of the mild changes. Bergstrom et al. (4) have reported that skeletal muscle glycogenolysis occurred during prolonged strenuous exercise and that development of severe muscle fatigue coincided with almost complete depletion of muscle glycogen stores. However, performance reduction or fatigue during infection in response to forced swimming could not be explained solely by exhaustion of skeletal muscle glycogen (Table 2), since data presented demonstrate a critical amount of glycogen (1 mg/g skeletal muscle and 0.6 mg/g carcass) found in working muscle of these infected rats. Blawacka et al. (5) suggested the involvement of some adaptive mechanism serving to conserve this indispensable residual glycogen store in the muscle. Results from the present study indicate that normal exercise induced glycogenolysis in heart, liver and muscle tissue of pre-agonal stage, infected-exercised rats.

Can alterations in circulating plasma lipids and hormone levels explain the observed decrease in swimming times of septic rats? Not directly. Exercise seemed to lessen the impact of infection-induced alterations in fat metabolism and hormone responses. While fasted-noninfected rats typically had increased plasma FFA and ketone bodies in conjunction with decreased plasma insulin and elevated plasma glucagon (2, 23), the fasted-infected rats demonstrated diminished plasma FFA and

ketone bodies and elevated insulin and glucagon concentrations (23). Swimming during sepsis in fasted rats amplified the ketone values and FFA depression, while causing a depression initially (up to 48 h) in both insulin and glucagon. At 72 h postinoculation, these hormone values were similar to fasted-infected-sedentary values and quantitatively indicated that these rats were not exercised to the same extent as rats at earlier stages in the disease process. It is likely that the regulation of fuel metabolism during infection and exercise is primarily influenced by a shift to anaerobic metabolism. This is supported by the decrease in glycogen stores, gluconeogenesis (31) and ketosis, the increase in hepatic ketogenesis coming from elevated lipolysis and FFA utilization under hormonal influence.

Results indicate that swimming exercise superimposed on pneumococcal infection does not alter the direction of infection-induced changes in substrate utilization, but does alter their magnitude of change. Alterations in fuel-hormonal metabolism cannot be directly related to infection-induced decrements in performance. This does not, however, rule out psychogenic reactions to illness (i.e., malaise and fatigue, commonly seen in man), fever-induced muscle protein wastage (2, 31), or cardiovascular impairment as alternative or contributing explanations for the observed reduction in physical work capacity.

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TABLE 1. Performance times of S. pneumoniae-infected and noninfected rats forced to swim for 2 h at various times postinoculation and post-starvation

Group	Time h	Swimming Time	% Decrease from Fed Rats
		min	
Fed-Exercised	0	> 120	
Fasted-Exercised	24	> 120	0
	48	118.2 \pm 8.0	2
	72	110.0 \pm 16.1	8
Fasted-Infected-Exercised	24	118.3 \pm 6.2	2
	48	89.5 \pm 15.0 [†]	26
	72	47.2 \pm 9.9 [†]	61

Numbers are means \pm SE of 10 rats. [†]P < 0.01 fasted vs. fasted-infected.

TABLE 2. Tissue glycogen concentrations in fed, fasted and fasted-infected rats compared to sedentary animals at various times postinoculation and poststarvation

Tissue	Group	Treatment	Glycogen Concentration (mg/g wet weight by h)			
			0	24	48	72
Heart	Fed	Sedentary	5.2 \pm 0.9			
		Exercised	4.0 \pm 0.6*			
	Fasted	Sedentary	3.3 \pm 0.4	5.8 \pm 0.3	7.5 \pm 0.2	
		Exercised	1.7 \pm 0.3*	2.4 \pm 0.2*	2.8 \pm 0.5*	
	Fasted-Infected	Sedentary	1.8 \pm 0.4†	2.7 \pm 0.3†	3.8 \pm 0.5†	
		Exercised	1.1 \pm 0.5*	1.2 \pm 0.3*	1.7 \pm 0.1*	
Liver	Fed	Sedentary	48 \pm 9			
		Exercised	32 \pm 4*			
	Fasted	Sedentary	3.4 \pm 0.9	3.0 \pm 0.6	3.0 \pm 0.3	
		Exercised	3.2 \pm 0.9	2.6 \pm 0.8	2.0 \pm 0.3	
	Fasted-Infected	Sedentary	0.8 \pm 0.1†	1.0 \pm 0.2†	1.7 \pm 0.7†	
		Exercised	0.7 \pm 0.1†	0.8 \pm 0.1†	1.2 \pm 0.02†	
Skeletal Muscle	Fed	Sedentary	5.5 \pm 0.4*			
		Exercised	3.2 \pm 0.8			
	Fasted	Sedentary	4.0 \pm 0.2	3.3 \pm 0.3	3.1 \pm 0.2	
		Exercised	3.1 \pm 0.9*	2.8 \pm 0.6	1.8 \pm 0.6*	
	Fasted-Infected	Sedentary	3.4 \pm 0.5	2.9 \pm 0.01	1.9 \pm 0.6	
		Exercised	1.2 \pm 0.4†	1.7 \pm 0.3†	1.3 \pm 0.2	

Carcass	Fed	Sedentary	3.3 \pm 0.3			
		Exercised	1.8 \pm 0.2*			
Fasted	Sedentary		1.6 \pm 0.2	1.5 \pm 0.06	1.2 \pm 0.1	
	Exercised		1.5 \pm 0.2	1.4 \pm 0.1	0.8 \pm 0.2	
Fasted-Infected	Sedentary		1.2 \pm 0.2	1.9 \pm 0.2	1.5 \pm 0.04	
	Exercised		0.7 \pm 0.02*†	0.6 \pm 0.03*†	0.6 \pm 0.02*	

Numbers are means \pm SE of 10 rats. * P $<$ 0.01 fasted vs. fasted-infected. † P $<$ 0.01 exercised vs. sedentary.

TABLE 3. Insulin:glucagon molar ratios of sedentary and exercised, fed, fasted and fasted-infected rats

Group	Treatment	Insulin:Glucagon Ratio by h			
		0	24	48	72
Fed	Sedentary	0.94 \pm 0.05			
	Exercised	0.40 \pm 0.02*			
Fasted	Sedentary		0.56 \pm 0.13	0.41 \pm 0.05	0.43 \pm 0.04
	Exercised		0.24 \pm 0.06*	0.34 \pm 0.01*	0.26 \pm 0.02*
Fasted-Infected	Sedentary		0.61 \pm 0.08	0.38 \pm 0.02	0.39 \pm 0.09
	Exercised		0.39 \pm 0.01†	0.47 \pm 0.03†	0.28 \pm 0.07

Numbers are means \pm SE of 10 rats. $^+$ $P < 0.01$ fasted vs. fasted-infected.

* $P < 0.01$ exercised vs. sedentary.

Figure Legends

FIG. 1. Febrile responses and plasma zinc concentrations in fed, fasted and fasted-infected sedentary and exercised rats. Each point represents the mean \pm SE of 10 rats. $^+P < 0.01$ fasted vs. fasted-infected. $^*P < 0.01$ exercised vs. sedentary.

FIG. 2. Influence of swimming exercise during infection on oxygen consumption in fed, fasted and fasted-infected rats. Each bar represents the mean \pm SE of 4 rats (separate study). $^+P < 0.01$ fasted vs. fasted-infected. $^*P < 0.01$ exercised vs. sedentary.

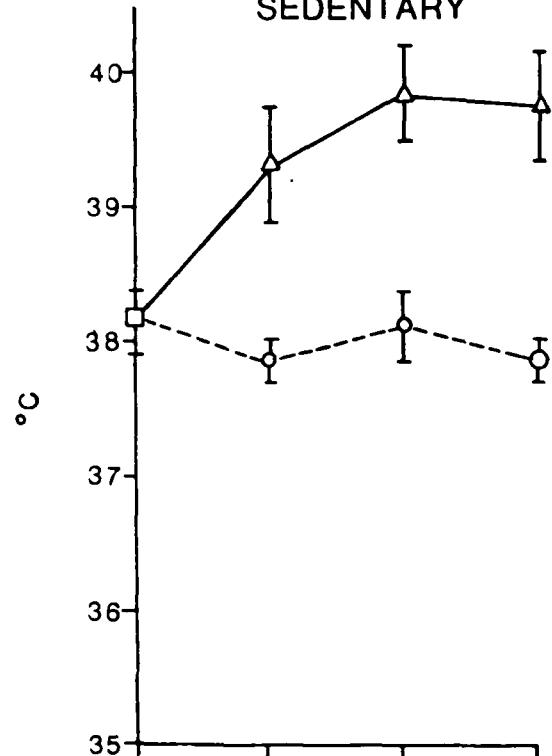
FIG. 3. Effect of exercise on blood lactate and plasma glucose values in infected and noninfected rats. Each point represents the mean \pm SE of 10 rats. $^+P < 0.01$ fasted vs. fasted-infected. $^*P < 0.01$ exercised vs. sedentary.

FIG. 4. Effect of exercise on free fatty acid and ketone body concentrations during S. pneumoniae infection. Each point represents the mean \pm SE of 10 rats. $^+P < 0.01$ fasted vs. fasted-infected. $^*P < 0.01$ exercised vs. sedentary.

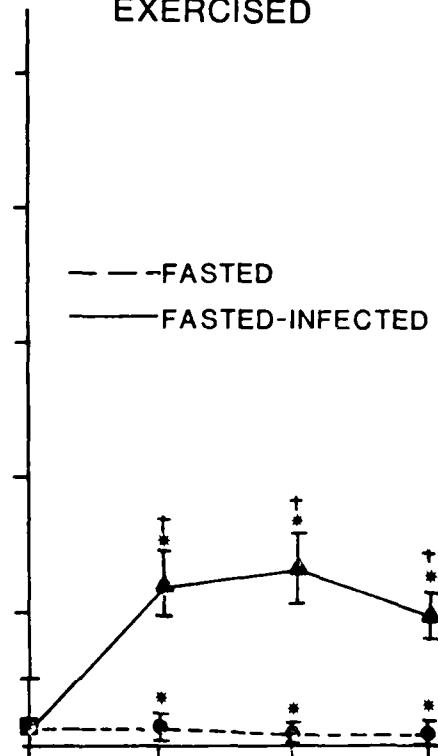
FIG. 5 Effect of exercise on plasma concentrations of insulin and glucagon. Each point represents the mean \pm SE of 10 rats. $^+P < 0.01$ fasted vs. fasted-infected. $^*P < 0.01$ exercised vs. sedentary.

RECTAL TEMPERATURE

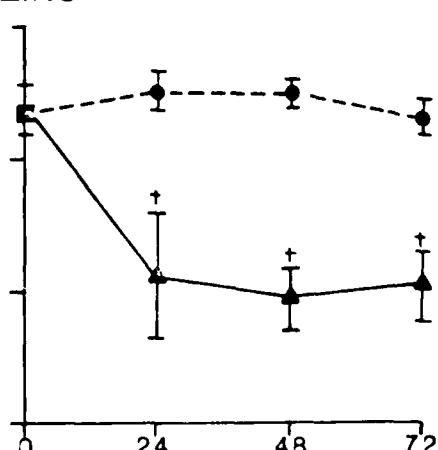
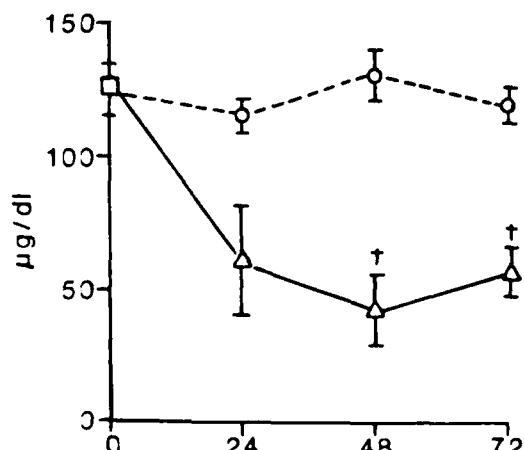
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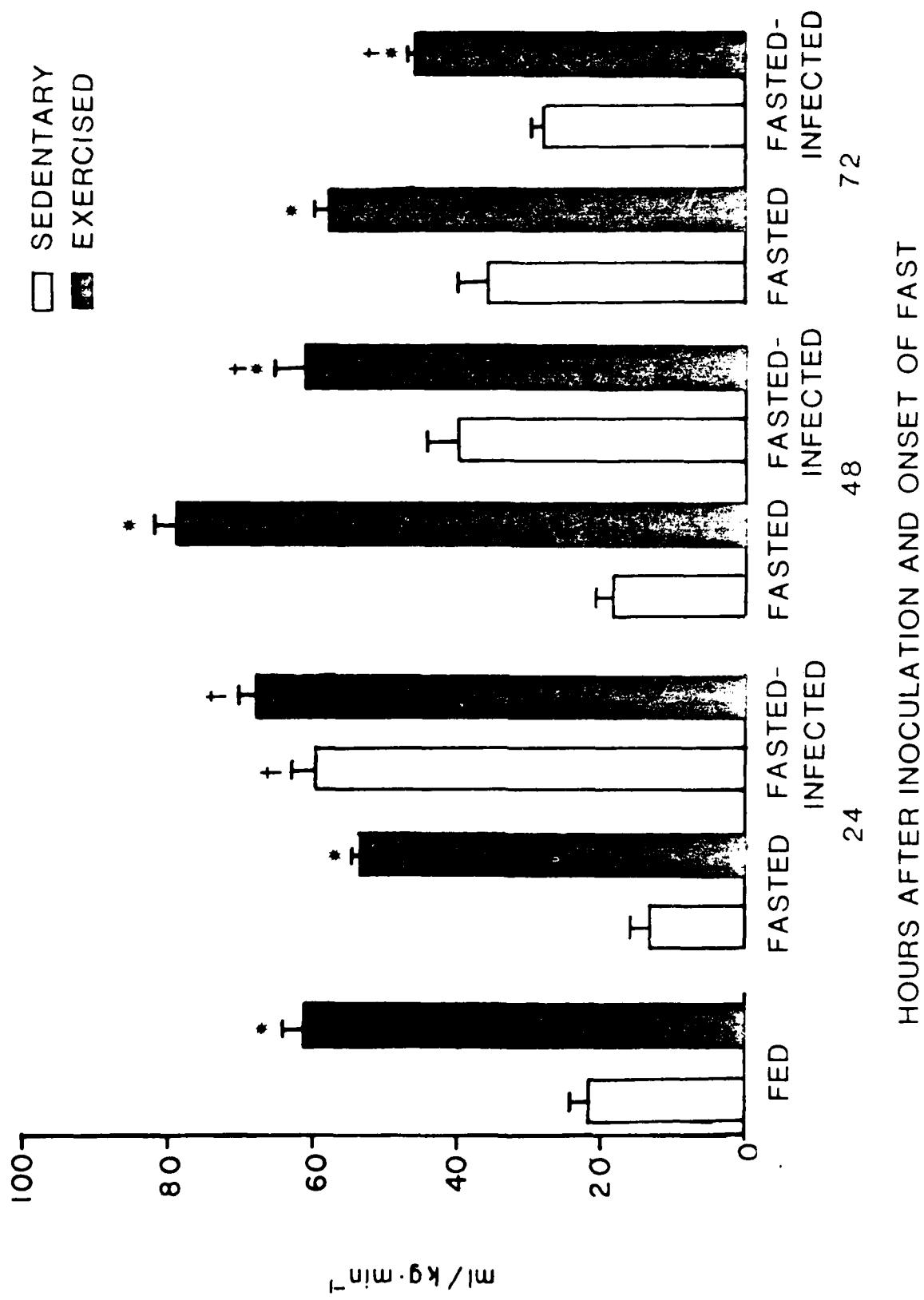
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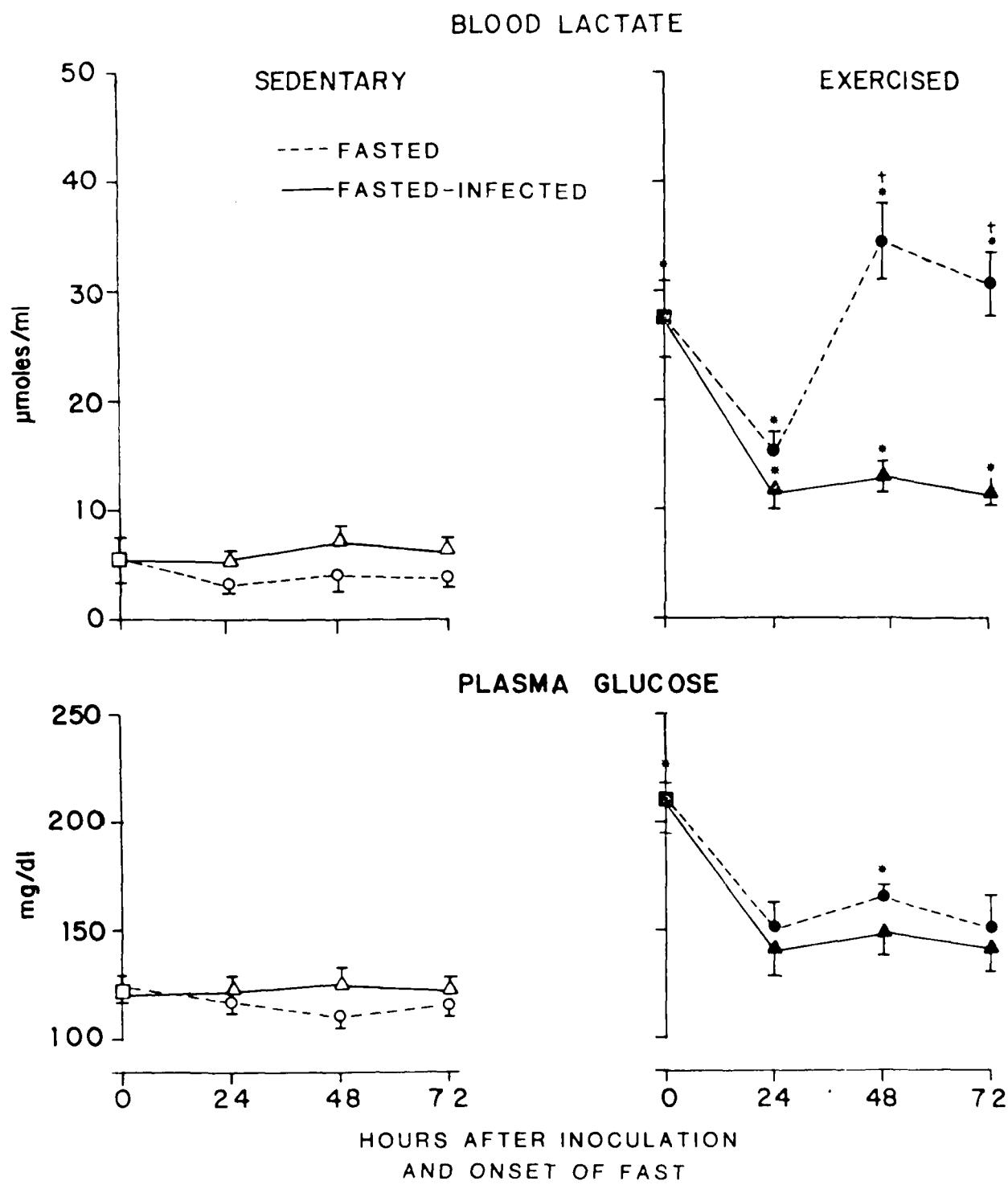


PLASMA ZINC



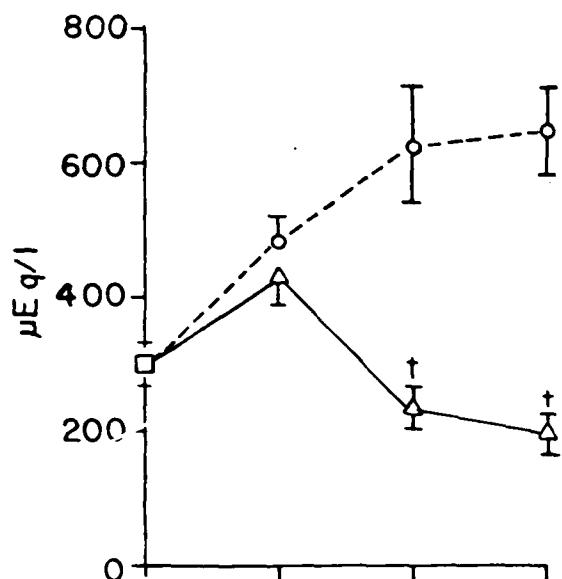
HOURS AFTER INOCULATION
AND ONSET OF FAST



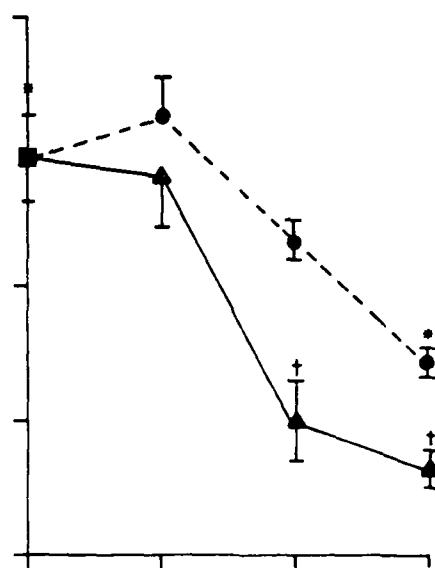


PLASMA FFA

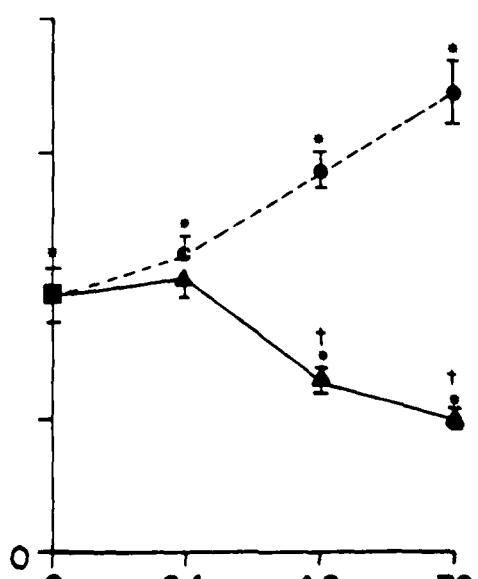
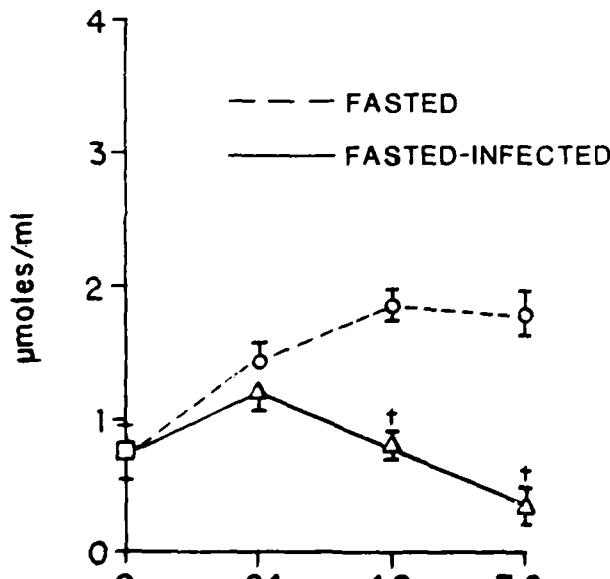
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EXERCISED



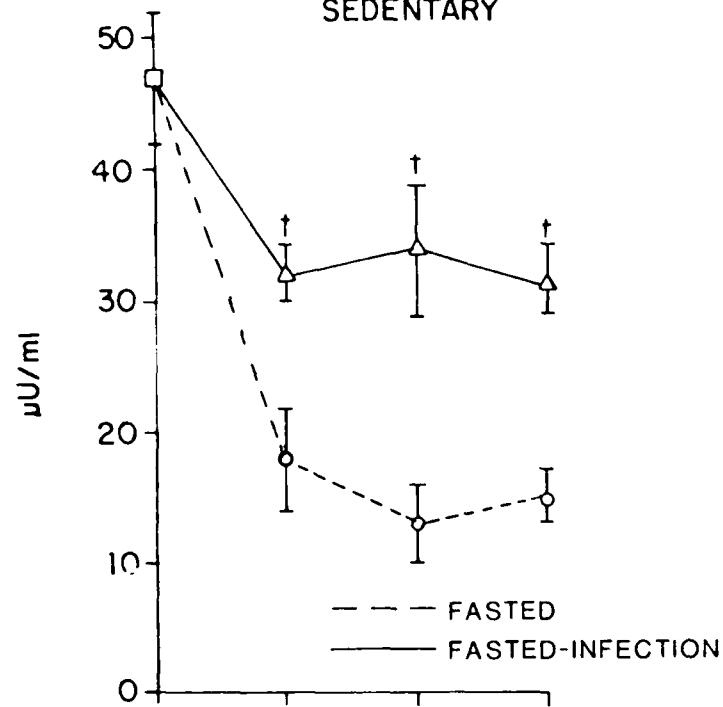
PLASMA KETONE BODIES



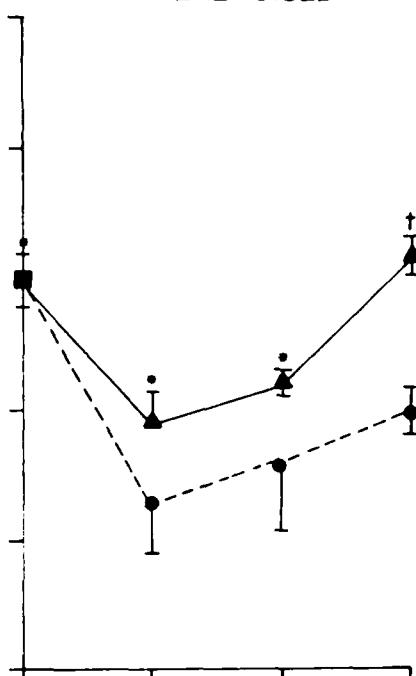
HOURS AFTER INOCULATION
AND ONSET OF FAST

PLASMA INSULIN

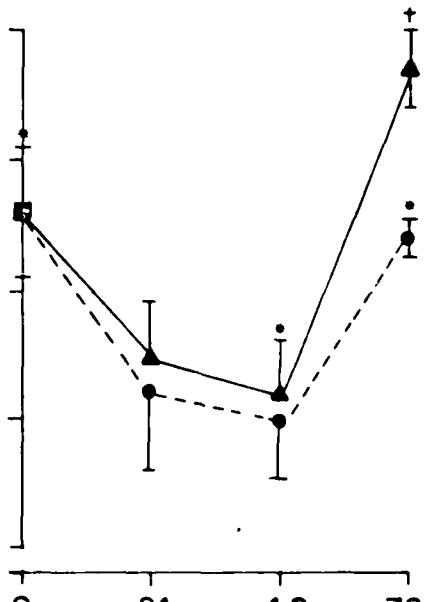
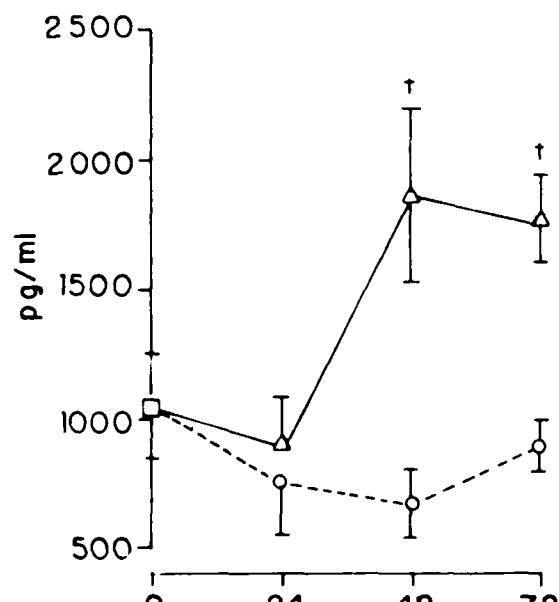
SEDENTARY



EXERCISED



PLASMA GLUCAGON



HOURS AFTER INOCULATION
AND ONSET OF FAST

